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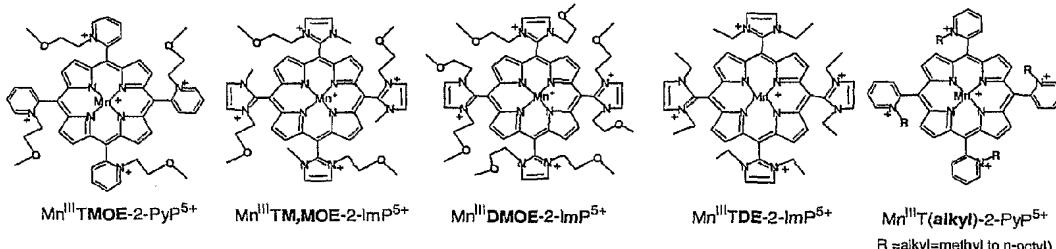
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(54) Title: SUBSTITUTED PORPHYRINS



Structures of the Mn(III) porphyrins studied

(57) **Abstract:** To improve bioavailability of the catalytic metalloporphyrin-based SOD mimics Mn(III) 5,10,15,20-tetrakis[N-ethylpyridinium-2-yl]porphyrin (MnTE-2-PyP<sup>5+</sup>) and Mn(III) 5,10,15,20-tetrakis[N,N'-diethylimidazolium-2-yl]porphyrin (MnTDE-2-ImP<sup>5+</sup>), three new Mn(III) porphyrins, bearing oxygen atoms within side chains, were synthesized and characterized: Mn(III) 5,10,15,20-tetrakis[N-(2-methoxyethyl)pyridinium-2-yl]porphyrin (MnTMOE-2-PyP<sup>5+</sup>), Mn(III) 5,10,15,20-tetrakis[N-methyl-N'-(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTM,MOE-2-ImP<sup>5+</sup>) and Mn(III) 5,10,15,20-tetrakis[N,N'-di(2-methoxyethyl)imidazolium-2-yl]porphyrin (MnTDMOE-2-ImP<sup>5+</sup>). The catalytic rate constants for O<sub>2</sub> dismutation (and the related metal-centered redox potentials vs NHE) for the new compounds are: log k<sub>cat</sub> = 8.04 (E<sub>1/2</sub> = +251 mV) for MnTMOE-2-PyP<sup>5+</sup>, log k<sub>cat</sub> = 7.98 (E<sub>1/2</sub> = +356 mV) for MnTM,MOE-2-ImP<sup>5+</sup> and log k<sub>cat</sub> = 7.59 (E<sub>1/2</sub> = +365 mV) for MnTDMOE-2-ImP<sup>5+</sup>. At 30 μM levels none of the new compounds were toxic, and allowed SOD-deficient *E.coli* to grow nearly as well as wild type. At 3 μM levels, the MnTDMOE-2-ImP<sup>5+</sup>, bearing an oxygen atom within each of the eight side chains, was the most effective and offered much higher protection than MnTE-2-PyP<sup>5+</sup>, while MnTDE-2-ImP<sup>5+</sup> was inefficient. These new porphyrins were compared to Mn(III) *N*-alkylpyridylporphyrins. While longer-chain *n*-alkyl members of the series exerted toxicity at higher concentration levels, they were very effective at submicromolar levels. Thus, 0.3 μM Mn(III) tetrakis(*N*-*n*-hexyl-pyridinium-2-yl)porphyrin and its *n*-octyl analogue offered the same level of protection as did ≥10 μM methyl and ethyl porphyrins. The k<sub>cat</sub> of methyl and *n*-octyl porphyrins are identical, but *n*-octyl is -10-fold more lipophilic. Therefore, the 30-fold improvement in bioavailability appears to be due to the increase in lipophilicity. MnTDMOE-2-ImP<sup>5+</sup> and longer-chain Mn(III) *N*-alkylpyridylporphyrins may offer better treatment for oxidative stress injuries than the previously studied MnTE-2-PyP<sup>5+</sup> and MnTDE-2-ImP<sup>5+</sup>.

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